REMARKS

Claims 75-76, 78-89 and 91 remain pending in this application. Claims 77 and 90 have been canceled. Claims 75-76 and 78-89 are currently amended and new claim 91 has been added.

Support for the amendments can be found in the specification and original claims as filed. Support for a "therapeutic" vaccine composition capable of "eliminating pre-existing tumors" and "protecting against a tumor relapse" can be found in the specification, for example, at page 11, lines 4-7; page 19, lines 9-11; and page 38, lines 1-9.

Support for "professional" antigen-presenting cells can be found in the specification, for example, at page 3, lines 20-22; page 10, lines 17-24; and page 13, lines 20-26. Support for "bcr-abl" fusion protein in new claim 91 can be found, in the specification, for example, at page 19, lines 21-24. No new matter has been added.

ALLOWABLE SUBJECT MATTER

At page 10, the Office Action acknowledges that claims 84 and 85 are allowed. In view of the amendments and the following remarks, Applicants submit that each of claims 75-76, 78-89 and 91 are allowable.

CLAIM OBJECTION

At page 2, the Office Action objects to claim 75 because of informalities. It appears the Office Action intended to reject claim 80. Accordingly, amended claim 80 addresses this issue and now recites "express a P2 receptor". Applicants request reconsideration and withdrawal of the objection.

CLAIM REJECTIONS - 35 USC § 103

At page 2, the Office Action rejects claims 75-79, 81, 82 and 86-90 under 35 U.S.C. § 103(a) as being unpatentable over KONTANI et al. (Cancer Gene Therapy (2002) 9:330-337), KIKUCHI et al. (Blood (2000) 96(1):91-99) and KRUG et al. (European Journal of Immunology (2001) 31:3026-3037).

At page 9, the Office Action further rejects claim 80 under 35 U.S.C. § 103(a) as being unpatentable over KONTANI, KIKUCHI and KRUG, in further view of NI et al. (Journal of Biological Chemistry (2002) 277)15): 12689-12696.

At page 9, the Office Action further rejects claim 83 under 35 U.S.C. § 103(a) as being unpatentable over KONTANI, KIKUCHI and KRUG, in further view FRITZ et al. (WO 02/069900).

Applicants respectfully traverse these rejections and address them together in the following remarks.

Present independent claim 75 is directed to a vaccine composition that includes a combined mixture of a nucleotide sequence encoding a tumor associated antigen and professional

antigen presenting cells (APCs). The APCs are in the form of dendritic cells expressing toll-like receptor 9 and modified to express one of CD40 ligand and GM-CSF. Also, the nucleotide sequence is provided in a vector that includes unmethylated CpG sequence. Independent claim 86 is directed to a method of producing such a vaccine.

KONTANI discloses the injection of a DNA vaccine (plasmid encoding MUC1 antigen). In their studies, KONTANI injected the DNA both alone and also together with a composition of non-primed dendritic cells (DCs) (see, Abstract).

First of all, in contrast to the presently claimed vaccine composition, the two constituents in KONTANI are inoculated in separate injections (see, Vaccination paragraph at pages 331-332). Indeed, the Office Action acknowledges that the two components in KONTANI are not mixed together in a combined mixture but "are administered separately". The Office contends, however, that this constitutes a mixture "*in situ*". Applicants respectfully disagree with this position. The separate administration of plasmid DNA and DCs at the vaccination site does not constitute a combined mixture, as recited in the present claims. Thus, KONTANI fails to teach or suggest providing and using a combined mixture of an antigen-encoding nucleotide sequence and antigen-presenting cells.

The vaccine composition according to the present claims involves a combined mixture of a vector having a nucleotide

sequence encoding a tumor associated antigen and a CpG sequence along with modified professional APCs. This combination enhances the CTL-priming effect of the vaccine as compared to a separate administration of the two constituents (as taught in KONTANI). Applicants assert that the presently claimed vaccine composition, having a combined mixture, can provide for activation of both innate and adaptive immunity, by binding of modified DCs and CpG-DNA-Ag, as presented in Figure 21.

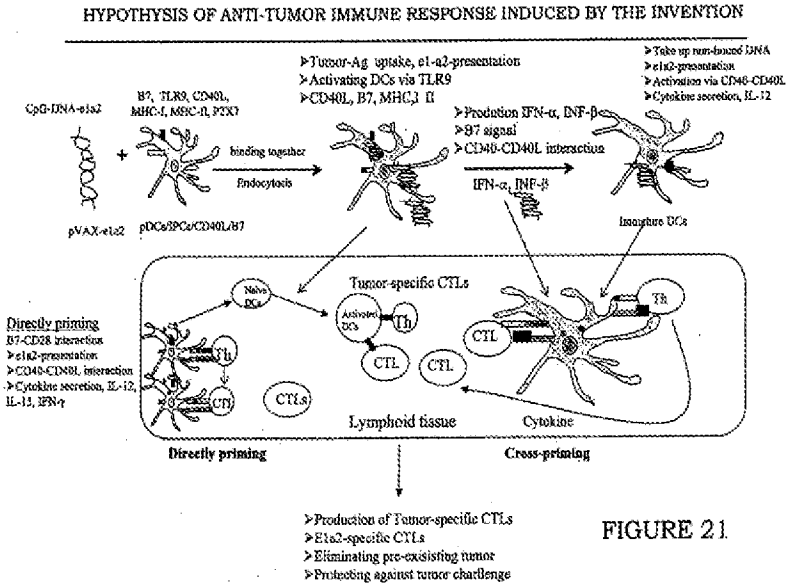

FIGURE 21

Secondly, the antigen-presenting cells in KONTANI are native dendritic cells, i.e., non-primed and non-modified dendritic cells (see, Abstract). KONTANI fails to teach or suggest a vaccine composition that includes antigen-presenting cells in the form of dendritic cells expressing toll-like receptor 9 and that are genetically modified to express CD40 ligand or GM-CSF from nucleotide sequences engineered into the cells.

Furthermore, the present composition is a "therapeutic" nucleotide vaccine composition capable of eliminating pre-existing tumors and protecting against tumor relapse. KONTANI fails to teach or suggest any vaccine composition having this type of activity. While KONTANI determined that sole injection of plasmid vector to vaccinate mice protected the mice against later challenge of cancer cells, the plasmid vector composition was not capable of suppressing tumor growth when injected into mice already bearing tumors (see, Abstract; Fig. 2, 3 and 4). When tumor-bearing mice received simultaneous injections of plasmid vector and native dendritic cells, some tumor growth suppressing effect was seen; however, 80 percent of the mice had died after only 45 days after tumor challenge (see, Fig. 5). Thus, while the KONTANI vaccination protocol perhaps showed a prophylactic effect to inhibit tumor formation, the vaccine failed to provide a therapeutic effect of eliminating pre-existing tumors and protecting against tumor relapse.

The Office Action appears to have misinterpreted the data presented in KONTANI. In Figure 1, KONTANI shows that vaccination with MUC1 DNA induces a higher level of anti-MUC1 antibody than vaccination with either MUC1 DNA with DC or with LacZ DNA. Contrary to the position taken in the Office Action at page 6, par. 3), Figure 1 does show the prevention of tumor growth. In Figure 2, KONTANI shows the proliferation of spleen cells (a mixture of many cell types) when co-culturing with

irradiated parental (EL4) or MUC-expressing EL4 (EL4-muc). Spleen cells from 4 out 6 mice vaccinated with MUC1 DNA showed elevated levels of proliferation in comparison to spleen cells from control plasmid (LacZ) DNA vaccination. One of ordinary skill in the art can see that the proliferation was poor (3000-4500 ^{3}H-TdUR, CPM). Once again, Figure 2 does not show the prevention of tumor growth.

The Office relies on KIKUCHI to teach modifying dendritic cells to express CD40L and contends that one of ordinary skill in the art would have been motivated to modify dendritic cells in this manner to enhance T-cell activation and anti-tumor antigen presentation. Applicants respectfully disagree with this conclusion.

KONTANI explicitly states that "*in vitro* preparation of DNA-transduced DCs, which involves separation of DCs from peripheral blood of cancer patients, transfection of DNA into the DCs, and then selection and propagation of the transduced DCs, is cumbersome, expensive, and needs a long time. This new DNA vaccination protocol combining DNA vaccine and naive DCs could overcome these difficulties, contributing greatly to the induction of strong antitumor immunity capable of suppressing tumor growth." (See, page 336, last paragraph, emphasis added). Thus, KONTANI teaches away from using any gene modified (DNA-transduced) dendritic cells because of the extra complexity, time and expense. Contrary to the position taken by the Office, one of

ordinary skill in the art would not have been motivated to include the teachings of KIKUCHI.

Furthermore, even if one did further pursue modification of dendritic cells, they would not have arrived at the presently claimed vaccine composition or method or preparation. KIKUCHI discloses that antigen-presenting cells in the form of dendritic cells are modified for expression of CD40 ligand encoded by a E1 adenoirus gene vector engineered into the antigen-presenting cells. (See, Abstract; page 91, right column, last line to page 92, first column, lines 1-2). Even by injecting the modified dendritic cells directly into the tumors, however, KIKUCHI achieved only a survival of as low as 20% of the test animals at week seven (see, Fig. 2).

Similar to KONTANI, any therapeutic effects achieved by the composition of KIKUCHI is moderate or poor. In other words, KIKUCHI does not offer any improvement compared to the composition of KONTANI. Thus, one of ordinary skill in the art would not have expected any improved vaccine composition from the combined teachings of KONTANI and KIKUCHI. Moreover, one would not have expected that any combination of KONTANI and KIKUCHI could produce a therapeutic nucleotide vaccine composition capable of eliminating pre-existing tumors and protecting against tumor relapse.

Because of the inferior results obtained in KIKUCHI, together with the teaching that KONTANI explicitly guides away

from using gene-modified dendritic cells, one of ordinary skill in the art would not have been motivated to combine these references.

Finally, the Office recognizes that KONTANI and KIKUCHI also fail to teach that the vector also includes a CpG sequence, as featured in the present claims, and relies on KRUG.

The Office contends that KRUG demonstrates a synergistic activation of plasmacytoid dendritic cells (PDCs) and the production of IL-12, IFN-α and bioactive IL-12 p70. The Office concludes that one of ordinary skill would have been motivated to modify dendritic cells to express CD40L and to add a CpG motif to the vaccine of KONTANI to induce synergistic activation of PDCs and production of IL-12.

While KONTANI and KIKUCHI describe vaccine compositions against tumor diseases, KRUG does not at all relate to tumor treatment. KRUG discusses the role of TLL receptors and in particular TLL receptor 9 (TLR9) in recognizing CpG DNA, which is a microbial stimulus (see, Abstract). KRUG speculates that TLR9 plays a role in detecting intraceullular pathogens, such as viruses, intracellular bacteria or parasites (see, page 3032, right column, last section). KRUG discloses that CpG sequences have been shown to protect mice against lethal infections with intracellular bacteria and parasites (see, page 3033, left columns, first section).

KRUG, however, fails to teach or suggest anything related to vaccine compositions or therapeutic vaccines capable of eliminating pre-existing tumors and protecting against tumor relapse, as featured in the present claims. The role of the CpG sequence and TLR9 as disclosed in KRUG is to trigger reactions in the human body that protects it against immediate bacterial/virus infections. For instance, the CpG-TLR9 interaction promotes and activates macrophages that are designed to phagocyte the invading bacteria and viruses. Again, this has nothing to do with any cancer disease. Furthermore, KRUG simply adds the CpG oligonucleotides to a cell culture solution in which the plasmacytoid dendritic cells are present (see, section 2.1). The CpG sequence in KRUG is not provided as part of a vector, as featured in the present claims.

Thus, because KRUG is directed towards intracellular pathogens and has nothing to do with cancer, one of ordinary skill in the art would not have combined the teachings of KONTANI and/or KIKUCHI with KRUG. In fact, such a combination could only have been made in hindsight with *ex post facto* analysis.

Finally, the combination of KONTANI, KIKUCHI with KRUG fails to teach or suggest a therapeutic nucleotide vaccine composition capable of eliminating pre-existing tumors and protecting against a tumor relapse. In fact, as disclosed in both KONTANI and KIKUCHI, their vaccine compositions were not capable of eliminating pre-existing tumors. The only results seen with

these compositions were a reduction in tumor growth; however, the tumors were still growing and still resulted in the death of up to 80 percent of the test animals. By comparison, the present vaccine composition achieved 100 percent test animal survival when administering the vaccine composition following tumor challenge and is therefore capable of eliminating pre-existing tumors (see, page 36, line 11-32).

In view of the amendments and the above remarks, KONTANI, KIKUCHI and KRUG fail to teach or suggest, and would not have rendered obvious, claims 75-79, 81, 82 and 86-90, as well as new claim 91. Accordingly, Applicants request reconsideration and withdrawal of this rejection.

The NI reference is applied in claim 80 in regard to APCs expressing a P2 receptor. The FRITZ reference is applied in claim 83 in regard to SEQ ID NO: 5. Neither of these references, however, overcome the deficiencies of KONTANI, KIKUCHI and KRUG detailed in the above remarks. Thus, the combination of KONTANI, KIKUCHI and KRUG, with NI or FRITZ, fail to teach or suggest, and would not have rendered obvious, claims 80 or 83. Accordingly, Applicants request reconsideration and withdrawal of these rejections.

CONCLUSION

Entry of the above amendments is earnestly solicited. Applicant respectfully requests that a timely Notice of Allowance be issued in this case.

Should there be any matters that need to be resolved in the present application, the Examiner is respectfully requested to contact the undersigned at the telephone number listed below.

The Commissioner is hereby authorized in this, concurrent, and future submissions, to charge any deficiency or credit any overpayment to Deposit Account No. 25-0120 for any additional fees required under 37 C.F.R. § 1.16 or under 37 C.F.R. § 1.17.

Respectfully submitted,

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